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# Indicator Exploration for Cancers in Women with Neurofibromatosis Type 1 - A Multi-Centre Retrospective Study

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## Abstract

**Objective:** Neurofibromatosis type 1 (NF1) is a complex hereditary syndrome with multi-systemic involvement and propensity to develop a variety of tumors. Despite the increased risk for malignant neoplasms and shortened life-span, there is no targeted cancer surveillance strategy. Clinical features of NF1 and family history may be associated with occurrence of certain neoplasms and serve as indicators for targeted surveillance.

**Methods:** This multi-centre retrospective study reviewed the records of 423 women with NF1. The associations between neoplasms, clinical features and family history were analyzed.

**Results:** The occurrence of breast cancers is positively associated (p = 0.004) with family history of any cancers, 9.6% (12/125) with family history vs. 2.7% (8/298) without. An association between NF1 clinical phenotypes (i.e. dermal neurofibroma burden) and cancer was not observed. However, the rate of malignant peripheral sheath tumor (MPNST) was significantly higher (p = 0.049) in women with plexiform neurofibroma (PN) than women without, 7.9% (11/139) vs. 3.14% (7/223). Women with learning disabilities have a higher rate (p = 0.019) of central nervous system (CNS) tumors including optic glioma (OPG) than women without, 22.2% (20/90) vs.11.2% (21/187). European Americans (EAs) are significantly more likely (p = 0.002) to develop CNS tumors (21.2%, 41/193) than African Americans (AAs) (6.8%, 6/88).

**Conclusion:** Family history of any cancers, preexisting PN, learning disability and EA ancestry is linked to higher risk of breast cancer, MPNST, and CNS tumors/OPG, respectively.

**Keywords:** Breast cancer; Central nervous system tumor; Clinical features; Family history; Learning disability; Optic glioma; Neurofibromatosis type 1

## Introduction

Neurofibromatosis type 1 (NF1) is a pleiotropic autosomal dominant hereditary syndrome. It is characterized by various types and numbers of benign and malignant neoplasms. The occurrence of gliomas, malignant peripheral nerve sheath tumors (MPNSTs), gastrointestinal stromal tumors (GISTs), and pheochromocytomas is significantly elevated compared to the general population [1,2]. The rate of colon and breast cancers are moderately increased, especially among individuals 50 years or younger [3-7]. A hospital admission based record-linkage population study has also shown an elevated risk for other common cancers, such as liver, esophagus, stomach, pancreas, biliary tract, lung, skin, thyroid, ovarian, leukemia and lymphoma in people with NF1 [8]. The spectrum of non-neoplastic clinical and physical features of NF1 is also wide. Despite the increased risk for malignant neoplasms, there is no established protocol to screen for cancer in people with NF1 beyond the guidelines for the general population. If any clinical features of NF1 and/or family history are found to be associated with occurrence of certain neoplasms, these may serve as indicators for targeted cancer or neoplasm surveillance. This multi-center case review study was designed to explore the associations between the occurrence of neoplasms and the physical/clinical features of NF1 in women with NF1. The overall goal is to identify factors associated with breast cancer in women with NF1.

## Material and Method

### Study subjects

Comprehensive medical record review was conducted in three Children's Tumor Foundation (CTF) affiliated neurofibromatosis clinics in the United States. These include Henry Ford Health System (HFHS), University of Alabama at Birmingham (UAB), and Johns Hopkins University (JHU). Children's National Medical Center

(CNMC) in the District of Columbia also recruited and collected medical information from affected mothers whose children were evaluated in the NF clinic. The medical records were reviewed for all females 20 years or older at the time of study, who either meet the consensus clinical diagnostic criteria of NF1 [9] or carry a deleterious mutation in the *NF1* gene. The four hundred and twenty three cases collected include all women who were seen in the clinic during the following periods of time: 114 cases (1994 to 2013) in HFHS, 122 cases (2011 to 2013) in UAB, and 156 cases (2003 to 2013) in JHU. In CNMC, 31 cases were collected from 2011 to 2013.

## Data collection

Demographic information gathered included date of birth, ethnicity, and biological relationships within the cohort. Medical information gathered included clinical features, such as the number of café-au-lait macules on the skin, presence of skin fold freckling, Lisch nodules on the irises, bony dysplasia, macrocephaly, short stature and learning disability. Neoplasm-specific information collected includes the number of cutaneous neurofibromas, plexiform neurofibromas (PN), optic gliomas (OPG), malignant peripheral nerve sheath tumor (MPNST), as well as other malignant solid tumors, malignant hematological disorders, malignant or benign tumor of the central nervous system (CNS). OPG is a tumor originated from neural glial astrocytes. It develops on the tract of optic nerve during the first several years in life. In this report, it is discussed as a separate entity from other CNS tumors.

For women identified as having breast cancer, the histological type, stage and age at diagnosis were recorded when available. Breast cancer screening and breast biopsy information was also collected. Family history information gathered included NF1, malignant neoplasm, CNS tumor, and the number of relatives with breast cancer based on three-generation pedigree obtained by a genetic counselor. Genetic test results such as *NF1* gene mutation and/or *BRCA1* and *BRCA2* mutation were documented when available. The occurrence of malignant neoplasms and CNS benign or malignant tumors were assessed for their possible association with clinical features associated with NF1. The CNS tumor category includes all tumors, from low grade glioma to high grade glioblastoma. A feature of thickened optic nerve or chiasm was not counted as OPG. The source of information and clinical features documented in the medical record was either self-reported by the patients or supported by clinical evidence.

## Statistical analysis

While an attempt was made to collect complete data on all subjects, the validity of multivariate analysis was limited due to missing data. Therefore, we have restricted the presentation of results to only those from the univariate analyses, assuming that the data for individual variables are missing completely at random. We used Fisher's exact tests to evaluate the statistical significance of association between each discrete clinical feature and prevalent cancers. P-values less than 0.05 were considered to be statistically significant. For ease of interpretability, odds ratios (OR) and corresponding 95% confidence intervals were also estimated to provide estimates of effect.

This research project has been prospectively reviewed and approved by the Institutional Review Board (IRB) of each participating centre and by the Human Research Protection Office (HRPO) of the U.S. Army Medical Research and Material Command.

## Results

A total of 423 cases of women affected with NF1 were reviewed. Average age for this cohort is 40 ± 14.7 years. Median age is 38 years. The study sample comprised 250 European Americans, 118 African Americans, and 41 individuals of other ethnicities. Ethnicity information was not available for 14 women. Thirty-six women are related to at least one other woman in this cohort and belong to a total of 16 kinships (Table 1). Family history of NF1 in female relatives was collected based on the pedigree in the medical chart. At least one female relative was affected with NF1 for 162 women. There were no female relatives affected with NF1 for 215 women. The status of family history of NF1 was not available for 46 women.

| Age Group | European American | African American | Others | Not available | E:A Ratio |
|---|---|---|---|---|---|
| All | 250 | 118 | 41 | 14 | 2.12 |
| 20-29 | 71 | 35 | | | 2.03 |
| 30-39 | 59 | 29 | | | 2.03 |
| 40-49 | 48 | 21 | | | 2.29 |
| 50+ | 72 | 33 | | | 2.18 |
| E:A ratio: European American to African American ratio | | | | | |

**Table 1:** Demographic distribution of all subjects.

At least one type of cancer was reported in 98 women with NF1. Nineteen of them have had at least two primary cancers. The breakdown of observed neoplasms is presented in Table 2.

| | Patients (n = 423) | % |
|---|---|---|
| **CNS tumor** | 18 | 4.30% |
| **OPG** | 41 | 9.70% |
| **CNS tumor and OPG** | 5 | 1.20% |
| **MPNST** | 22 | 5.20% |
| **GIST** | 6 | 1.40% |
| **Breast** | 20 | 4.70% |
| **Other Neoplasms** | 13 | 3.10% |
| **Plexiform Neurofibroma** | 142 | 33.60% |
| CNS: Central Nervous System | | |
| OPG: Optic Glioma | | |
| MPNST: Malignant Peripheral Nerve Sheath Tumor | | |
| GIST: Gastrointestinal Stromal Tumor | | |

**Table 2:** Distribution of neoplasms in women with NF1.

There were 205 prevalent cancer/neoplasms in the relatives of 125 women with NF1. These included 9 NF1 related cancers (consisting of brain tumor and MPNST), 4 neuroendocrine tumors (consisting of pheochromocytoma and pituitary tumor), 4 sarcomas, 8 hematological

cancers, 75 breast cancer, and 105 other cancers (consisting of 21 lung, 18 colorectal, 4 esophageal, 2 gastric, 6 head and neck, 3 cervical, 5 ovarian, 3 uterine, 3 bladder, 12 prostate, 3 renal, 9 skin or melanoma, 3 pancreatic, 3 thyroid, 6 "bone", 2 "thoracic" cancer and 1 metanephric stromal tumor).

## Breast cancer

Of the 20 women who have a personal history of breast cancer, 15 were previously reported by Wang [5] and Madanikia [6] in 2012. Eleven are European Americans and 8 are African Americans. Ethnicity information for the remaining individual is not available (Table 3). None of these women are known to be genetically related to one another. Half of the cases (n = 10) were diagnosed with breast cancer between the age of 40 to 49 years. A quarter of the cases (n = 5) were diagnosed between 30 to 39 years of age. Two cases were diagnosed with a second primary breast cancer.

| ID | Age at Diagnosis Breast Cancer | Family History | | |
|---|---|---|---|---|
| | | Any Cancers | Breast Cancer | NF1 |
| 1 | 29 | + | + | + |
| 2 | 39 | + | + | + |
| 3 | 39 | + | unknown | unknown |
| 4 | 41 | + | + | - |
| 5 | 43 | + | - | - |
| 6 | 44 | + | + | + |
| 7 | 49 | + | + | unknown |
| 8 | 49 | + | + | - |
| 9 | 57 | + | - | + |
| 10 | 70 | + | unknown | unknown |
| 11 | unknown | + | + | + |
| 12 | unknown | + | + | - |
| 13 | 34 | - | - | - |
| 14 | 37 | - | - | unknown |
| 15 | 40 | - | - | + |
| 16 | 43 | - | - | + |
| 17 | 47 | - | - | + |
| 18 | 47 | - | - | - |
| 19 | 49 | - | unknown | + |
| 20 | unknown | - | unknown | unknown |
| +: Yes -: No | | | | |

**Table 3:** Family history and age at the diagnosis of breast cancer.

All of these breast cancers are ductal carcinoma, except one invasive lobular carcinoma, which is estrogen receptor (ER) positive (Table 4). Only one case was known to be an ER-PR (estrogen-progesterone receptor) negative and HER2 expression negative (i.e. triple negative) invasive ductal carcinoma. Two cases are known to be ER-negative, HER2 expression positive tumors.

| | Invasive (n) | in situ (n) | N/A (n) |
|---|---|---|---|
| **Total** | 8 | 6 | 6 |
| **Ductal** | 6 | 6 | 8 |
| **ER+** | 4 | 0 | 13 |
| **ER--** | 2 | 1 | |
| **Her2+** | 1 | 1 | 15 |
| **Her2--** | 3 | 0 | |
| **Stage** | | | |
| **1** | 2 | | |
| **2** | 1 | | |
| **3** | 5 | | |
| **4** | 0 | | |

**Table 4:** Histological types of the breast cancer.

## Breast cancer and family history

The prevalence of personal history of breast cancer was nearly four-fold higher (odds ratio OR = 3.83, 95% confidence interval 95%CI = 1.40-11.12) for women with NF1 and a family history of any cancers (9.6%; 12/125) in comparison to those without a family history (2.7%, 8/298), which was statistically significant (p = 0.004). The type of cancers in the family history does not differ significantly between the women with breast cancer and those without. However, when there is a family history of 3 or more cancers, the rate of personal breast cancer is 4 times higher (26.3% 5/19) than the rate when there are only 1 or 2 cancers in the family (6.6% 7/106), p = 0.019. The prevalence of personal breast cancer with a family history of breast cancer in 1st, 2nd, and 3rd degree female relatives (10.7%, 8/75) is more than 3-fold higher (OR = 3.46; 95%CI = 1.09 - 11.02) than without a family history (3.3%, 8/241), which is statistically significant (p = 0.029). However, breast cancer is not significantly associated with family history of female relatives with NF1 (p = 0.434). In this cohort, none of the women with breast cancer had a reported family history of any relative affected with NF1 and breast cancer.

## Breast cancer and clinical features of NF1

For cases with available clinical features, statistical analysis has not detected any association between the NF1 features, breast cancer or other cancers (all p ≥ 0.16, Supplementary table 1). It is noteworthy to mention that high cutaneous neurofibroma burden (20 or more or described as "diffuse" in the medical record) is not significantly associated with any types of cancer (p = 1.00).

## MPNST and plexiform neurofibroma

The occurrence of MPNST is related to plexiform neurofibromas (PN). Among women with documented PN, 7.9% (11/139) have a history of MPNST, which is significantly higher (p = 0.049) than the women without, 3.14% (7/223).

### CNS tumor, optic glioma (OPG) and learning disability

The prevalence of CNS tumors is significantly higher (p = 0.004) in women with a history of OPG (14.6%, 6/41) in comparison to women without OPG (2.9%, 8/278). The women with learning disability have a 2.25-fold (95%CI = 1.08-4.67) higher rate of CNS tumor, OPG or both (i.e. "CNS+OPG") (22.2%, 20/90) than those without a learning disability (11.2%, 21/187), which is significant (p = 0.019). Due to the small number of cases, the relationship between learning disability and CNS tumor excluding OPG cannot be determined at this time. However, upon exclusion of the cases with CNS tumor alone, the association between learning disability and OPG with or without CNS tumors is suggestive, but not statistically significant in this cohort, 16/90 vs. 19/187, p = 0.083.

### Ethnicity and malignant neoplasms

The rate of "CNS+OPG" and "Other cancers" varies significantly by ethnicity. "Other cancers" refers to all malignant tumors, hematological malignancies, CNS tumors and OPG, excluding breast cancer. For the "CNS+OPG" category, European Americans (EAs) were 3.72 times (95% CI = 1.48 -11.16) more likely to develop these tumors (21.2%, 41/193) than African Americans (AAs) (6.8%, 6/88), which was statistically significant (p = 0.002). The occurrence of OPG with or without CNS tumor is also higher (OR = 3.48, 95%CI = 1.28 - 11.88, 95%) in EAs (17.4%, 32/184) than AAs (5.7%, 5/88), which was significant (p = 0.008), For the "Other cancers" category, EAs were also significantly (p = 0.004) more likely to develop these tumors (26.8%, 67/250) than AAs (13.5%, 16/118). Analysis could not demonstrate a statistically significant association between ethnicity and breast cancer (p = 0.301).

### Ethnicity and other clinical features

Lisch nodules are more common in EAs (59%, 100/170) relative to AAs (39%; p = 0.009, 26/66) or other ethnicities (32%; p = 0.010, 10/31). There is also a significant difference between the number of individuals with higher dermal neurofibroma burden, i.e. 20 or more or described as "diffuse" at the time of clinical evaluation, by ethnicity, with AAs having a higher rate (75.8%, 47/62) of high tumor burden than EAs (53.0%, 70/132; p = 0.003).

## Discussion

The multi-systemic involvement of NF1 and apparent physical signs has had inspired studies to investigate the association between these signs to shed light on the underlying molecular mechanisms [10,11]. The current study aimed at finding the association between physical signs, clinical features, family histories and malignant neoplasms. The strength of this study is that it is a multi-center study representing an adult NF1 patient population from widespread geographical areas within the United States (Baltimore and Washington D.C. on the east coast, Detroit in the Mid-West and Birmingham of Alabama in the South). The percentage of African Americans in this study is higher relative to most other studies, thus providing a novel insight into the clinical profile of NF1 in this population. The weakness of the study is that it is a retrospective study with its associated biases. Data regarding screening, detection and treatment of cancers other than breast, was not collected. Additionally, the study cohort represents individuals with NF1 seeking care in a large academic and/or tertiary care center in adulthood, likely with relatively severe disease manifestations or morbidity. Family history recall by patients may be biased by personal health situations occurring at the time the pedigree was obtained. In addition, only female cases were analyzed.

Previous studies have revealed a significantly elevated breast cancer risk, 4-8 fold, in women with NF1 under age 50 in England and the United States [3-7]. For women age 50 or older, the risk is also elevated, but to a lesser degree, 1.9-2.6 fold. This phenomenon leads to the suspicion that a pathogenic germline *NF1* genetic variant may be an independent risk factor for breast cancer. Based on this assumption, family history of NF1 should be associated with breast cancer in this population. However, this hypothesis is not supported by the results of this study. This study demonstrates that a personal history of breast cancer in women with NF1 is associated with a family history of breast cancer (OR = 3.46) or all cancers (OR = 3.83) but does not appear to be associated with family history of NF1 alone in female relatives. Nevertheless, we cannot exclude the possibility that the association between personal history of breast cancer and family history of breast cancer is enhanced by family history recollection bias. It is possible that patients who had a personal history of cancer were more likely to report a family history of cancers during the pedigree collection. Additionally, we cannot exclude the possibility that the lack of association between personal history of breast cancer and family history of NF1 may be partially due to the following two factors: 1) The study may lack sufficient statistical power due to the small sample size. 2) Breast cancer may not have manifested itself yet in some of the female relatives with NF1. The ages of relatives with NF1 were not collected therefore the percentage of relatives under age 30 is unknown. Nevertheless, a general population study utilizing a Swedish database has previously characterized the elevated breast cancer risks in association with family history of breast cancer in first and second degree relatives. The relative risk (RR) was 1.27 when a sister was affected. The RR was 1.74 when a mother was affected. The RR was 2.8 when at least 2 first degree female relatives were affected [12]. This association appears to be at a lesser degree than was observed in our cohort of NF1, however, the family histories in our study included all first, second and third degree relatives and were not stratified based on the degree of relationship. It is unclear at this time whether the higher prevalence of breast cancer in NF1 is a result of a dysfunctional *NF1* gene, environmental carcinogens and/or other hereditary cancer predisposition genomic variants or a synergistic effect between these three factors. The pattern of non-breast cancers in the family history offers no clue as what sort of carcinogens or hereditary genomic predispositions may be involved. No germline mutations in hereditary high penetrance breast cancer genes, *BRCA1* or *BRCA2*, have been reported in the 20 cases of breast cancer. Exploration of the co-occurring germline genomic mutations or variants may provide further clues. Germline Whole Exome Sequencing (WES) in a series of 14 NF1 women affected with breast cancer has been completed by Wang and colleagues. Five of the cases are from the current study. Preliminary analysis showed no deleterious mutations in *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*, *PALB2*, *STK11* or *PALB2* genes. Based on the current data, the use of family history of breast cancer or any cancers as a risk indicator for personal breast cancer in women affected with NF1 may be a valuable tool.

The distribution of the histological types and hormonal receptor status for the breast cancers in women with NF1 does not differ significantly from the general population, except ER-negative tumors are under represented. Another manuscript will explore this in detail.

Whenever there is a heavy cutaneous neurofibroma burden, dermal neurofibromas on the breasts may be seen. Multiple bilateral dermal

neurofibromas may be categorized as benign on mammography, with the relevant clinical history. Neurofibromas within the breast parenchyma are also common and may present as a new mammographic mass or a newly palpable finding on physical examination by the patient or health care provider. For neurofibroma within the parenchyma, physical examination may not reliably distinguish it from a primary breast malignancy. Based on the current standard of care, palpable findings in women over the age of 30 should be evaluated with mammography and ultrasound. On mammography and ultrasound, neurofibromas within the breast commonly present as a non-calcified solid mass with a round or oval shape and circumscribed or obscured margins. If deemed probably benign based on imaging criteria, neurofibromas within the breast may require subsequent follow up imaging. Similar to mammography and ultrasound, limited data exist regarding reliable differentiation of neurofibromas from invasive breast cancers based upon morphology and enhancement kinetics on MRI. However, for a neurofibroma with a myxoid matrix, the high T2 signal intensity of neurofibromas is a classic feature in the correct clinical setting [13]. Whether or not breast MRI may be valuable to reduce biopsies of palpable neurofibromas or as a supplemental screening modality in women with NF remains to be explored.

The association between MPNST and plexiform neurofibroma supports the previous evidence that the majority of MPNSTs emerge from preexisting plexiform neurofibroma [1,14]. Therefore, preexisting PN may also serve as a risk indicator for MPNST.

The current study suggests that OPG during childhood may serve as a risk indicator for future occurrence of brain tumor in individuals with NF1. The association between OPG and brain tumor has been reported by Singhal and colleagues where 17 cases of NF1 related OPG were followed prospectively [15]. However, our study was not designed to collect the timing of diagnosis or the character or treatment of OPG. Asymptomatic OPG or other low grade CNS glioma without progression or a need for treatment may have been an incidental finding when brain was imaged for other reasons. Therefore, we cannot exclude the possibility that at least two factors have partially contributed to the association: 1) Asymptomatic OPGs were discovered during other CNS tumor evaluation, or vice versa; 2) Radiation therapy for OPG induced the CNS tumor later in life. An increased rate of CNS tumors later in life was previously reported among patients who have had radiation therapy for OPG [15,16]. The current standard is to avoid using radiation therapy for OPG in individuals with NF1.

Our study demonstrated an association between learning disability and CNS and/or OPG tumor, an observation also reported previously [15,17]. This association suggests a common defect hindering the CNS development congenitally as well as predisposing to CNS tumor formation later in life. In individuals with NF1, OPG mostly occurs during early childhood. As treatment for OPG, chemotherapy or radiation is known to have adverse effects on the developing brain, leading to learning disability. In a recent 20 year-perspective study of OPG, 149 children were diagnosed with OPG by MRI screening. Only 22 children required treatment [18]. Nevertheless, learning disability as a side effect of OPG treatment and/or a large tumor altering brain function could have partially contributed to the association between these two variables. More advanced study with information regarding OPG treatment, as well as metrics assessing learning disability before and after CNS or OPG treatment will allow us to better characterize the relationships.

Our study shows that predisposition to CNS tumors and/or OPG is disproportionally higher in European Americans, in comparison to African Americans. Although the observation in this study could be compounded by the possible unequal access to brain imaging between races, we do not believe the higher frequency of tumor in EAs is entirely resulted from easier access. A prior report of smaller sample size in 1998 suggested a similar predilection for OPG in EAs versus AAs [19]. A recent larger cohort retrospective study has also demonstrated this phenomenon [18]. This trend coincides with the observations that the incidence of sporadic malignant CNS tumor in non-Hispanic whites is around 2-4 times that of blacks in North America [20]. All of above suggests that the CNS tumor or OPG in NF1 patients may share a common pathway in tumorigenesis as sporadic brain tumors. As such, European American ethnicity may be a risk indicator for brain tumor in the population with NF1. However, in the absence of additional data, including grade, progression, and the need for treatment in these brain tumors, the life-time risk and the need for screening cannot be adequately evaluated.

## Conflict of Interest

Dr. Xia Wang has no conflicts to disclose.

Renée N. Tousignant has no conflicts to disclose.

Dr. Albert M. Levin has no conflicts to disclose.

Dr. Bethany Niell has no conflicts to disclose.

Dr. Maria T. Acosta has no conflicts to disclose.

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